Beta-blockade at low doses restoring the physiological balance in myocytic antagonism

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Beta-blockade at low doses restoring the physiological balance in myocytic antagonism☆

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Abstract

Objective: The ventricular mass is organized in the form of meshwork, with populations of myocytes aggregated in a supporting matrix of fibrous tissue, with some myocytes aligned obliquely across the wall so as to work in an antagonistic fashion compared to the majority of myocytes, which are aggregated together in tangential alignment. Prompted by results from animal experiments, which showed a disparate response of the two populations of aggregated myocytes to negative inotropic medication, we sought to establish whether those myocytes that aggregated so as to extend obliquely across the thickness of the ventricular walls are more sensitive to beta-blockade than the prevailing population in which the myocytes are aggregated together with tangential alignment. If the two populations respond in similar differing fashion in the clinical situation, we hypothesize that this might help to explain why drugs blocking the beta-receptors improve function of the ventricular pump in the setting of congestive cardiac failure. **Methods:** We implanted needle probes in 13 patients studied during open heart surgery, measuring the forces generated in the ventricular wall and seeking to couple the probes either to myocytes aggregated together with tangential alignment or to those aggregated in oblique fashion across the ventricular walls. In a first series of patients, we injected probatory doses intravenously, amounting to a total bolus of 40–100 mg Esmolol, while in a second series, we gave fixed yet rising doses of 5, 10, and 20 mg Esmolol in three separate boluses. **Results:** Forces recorded in the aggregated myocytes with tangential alignment decreased insignificantly upon administration of low doses (57.1 ± 12.4 mN $\rightarrow$ 56.6 ± 7.6 mN), while forces recorded in the myocytes aggregated obliquely across the ventricular wall showed a significant decrease in the mean (59.3 ± 11.6 mN $\rightarrow$ 47.4 ± 6.4 mN). **Conclusions:** The markedly disparate action of drugs blocking beta-receptors at low dosage seems to be related to the heterogeneous extent, and time course, of systolic loading of the myocytes. This, in turn, depends on whether the myocytes themselves are aggregated together with tangential or oblique alignments relative to the thickness of the ventricular walls.

Keywords: Beta-blockade; Intrinsic antagonism; Auxotonic forces; Unloading forces

1. Introduction

In previous studies [1–3], we have shown that the ventricular myocardium is organised in the form of a three-dimensional mesh of myocytes set in a supporting matrix of fibrous tissue. The myocytes within this mesh are able to function in antagonistic fashion. This is because the prevailing mass of myocytes, aggregated together with their long axes tangential relative to the thickness of the ventricular walls, is responsible for overall constriction of the ventricular cavity. The opposing arm of the dualistic system is provided by a population of myocytes, present throughout the myocardial mesh, which are aggregated such that their long axes are oblique across the thickness of the wall, running in the direction from the epicardium to the endocardium [2,3]. In the normal heart, this population of obliquely orientated aggregates of myocytes, besides sustaining ventricular constriction, also has the function of attenuating the marked systolic mural ventricular thickening [1–3], thus preserving the shape and size of the ventricular

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cavity. In one of our previous studies [1], we showed that the population of obliquely orientated myocytes is more sensitive to the negative inotropic action of barbiturates than are the myocytes that are aggregated with their long axes tangential to the ventricular walls. In this investigation, we have continued to explore the action of drugs on the two populations of myocytes, assessing in this instance the disparate action of the ultra-short-acting blocker of beta-receptors, Esmolol [4], known to exert a negative inotropic effect.

In this respect, it has now been shown that several months of medication with beta-blockers unexpectedly reduces morbidity and mortality in patients with mild-to-moderate chronic cardiac failure [5—9]. Independent of these late beneficial effects of beta-blockade, we hypothesize that an initially weak heart benefits instantaneously from treatment with low doses of drugs that block the beta-receptors, since we expect the drug to reconcile the pre-existing unbalance of action of the intrinsic antagonistic structure and function. This is because the beta-blockade attenuates instantly, and in more efficient fashion, the forces produced by the myocytes aggregated with their long axes oblique relative to the thickness of the ventricular walls, as opposed to the constrictive forces provided by the myocytes aggregated with their long axes tangential to the ventricular wall.

2. Methods

During an extensive cardiodynamic study on the effect of partial left ventriculectomy [10], we had the opportunity to investigate also two small cohorts, comprising patients undergoing treatment with Esmolol while undergoing various kinds of cardiac surgical procedures. The patients making up our first cohort served as a pilot series to establish the appropriate dosage of Esmolol. All patients were Caucasian, three male, two female, aged from 57 to 74 years, with a mean age of 65.8 years, and all were studied during preparation for coronary arterial surgery. All patients gave informed consent consistent with the institutional policy of the Academic Hospital, University of Pretoria, South Africa. While maintaining standby extracorporeal circulation, we implanted two force probes [1] into the base of the left ventricle, one placed close to the atrioventricular junction and the second in the mid-portion of the ventricle (Fig. 1). The probes were implanted almost parallel, yet slightly inclined with respect to the epicardium. Although there is no way to predict the alignment of the aggregated myocytes by visualising the epicardial ventricular surface, we sought to couple, in each patient, one probe to the population of obliquely intruding myocytes aggregated in oblique direction from the endocardium to the epicardium [3,4], and which are known to produce an auxotonic force signal [1]. It was then our intention to couple the other probe to the prevailing population of myocytes, which are aggregated with their long axes tangential relative to the thickness of the wall, and which produce an unloading type of force signal (Fig. 2). In two of the five patients, however, we recorded auxotonic signals from both probes (Table 1). We also measured arterial pressure in the radial artery as is routinely done during cardiac surgery. After a control recording, we administered

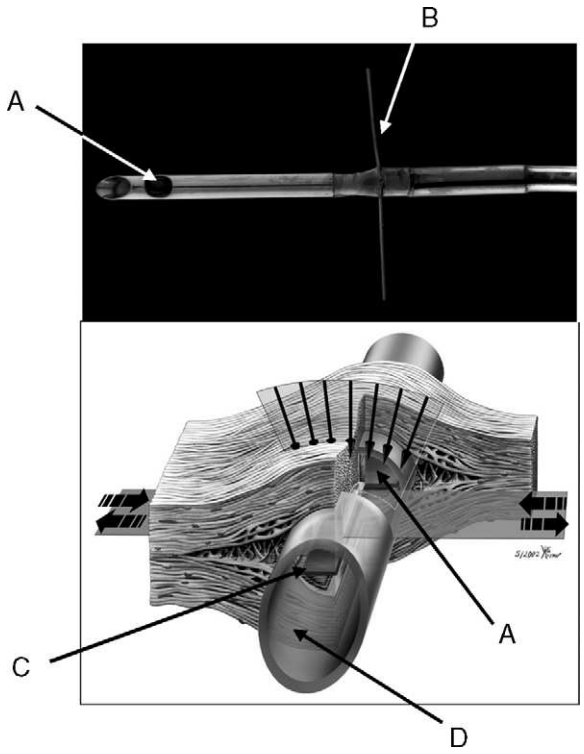

Fig. 1. The needle force probe (upper panel), 1.5 mm thick and 9 mm long, is designed with a lateral window (A) containing the flexural bar (not visible). The fine bar (B) crossing the base at right angles serves to stabilize the probe against rotation on the epicardial surface. The lower panel shows how the probe measures the forces within the slightly spread three-dimensional meshwork of myocytes. Some of the myocytes impinge through the lateral window (A) on the flexural bar (C), which is then deviated from its central position within the lumen of the needle (D) by forces (fine arrows) engendered by the myocytes while they contract in axial direction (bold arrows). This deviation is sensed by a pair of strain gauges (not shown) glued to the flexural bar.

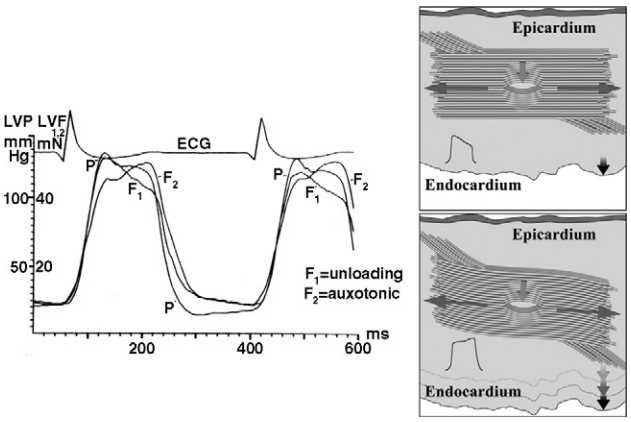

Fig. 2. The left panel shows simultaneous recordings of the electrocardiogram (ECG), left ventricular pressure (*P*), and an unloading type of force signal (F_1), which declines during ventricular ejection, as opposed to an auxotonic, or augmenting, type of signal (F_2), which continues to rise throughout ventricular ejection, outlasting the period of ejection. In the right panel, it can be seen that the type of signal is the function of the angulation of the aggregated myocytes to which the flexural bar within the probe is coupled relative to the epicardial surface. In the upper section, the alignment of the myoctes is parallel to the epicardium, while in the lower panel, the myocytes are aligned with an inclined angle relative to the epicardium. Our intention is to achieve an unloading type of signal with the arrangement shown in the upper panel, and an auxotonic signal with the angulation illustrated in the lower panel.

Table 1
The alterations in haemodynamic and cardiodynamic conditions induced by pilot doses of Esmolol given to five South African Caucasian patients

Patient number	Gender	body weight (kg)	Age	Surgery	Esmolol (mg/dose)	LVP/AP (mmHg) cont.->MDE	LVEDP/AP $_{diastol}$ (mmHg) cont.->MDE	Developed Force (subbasal) cont.->MDE	Developed Force (mid-portion) cont.->MDE	Heart rate (b/min) cont.->MDE
Caucasian Patients										
1	male	87	63	coronary	100	110->75	51->33	**45->35**	51->30	74->68
2	male	75	65	coronary	50	95->95	46->46	**55->54**	56->34	74->66
3	female	82	70	coronary	50+50	148->71	54->28	58->40	66->55	85->74
4	female	65	74	coronary	25+25+50	110->105	63->59	61->51	72->55	97->82
5	male	84	57	coronary	40	138->96	92->46	71->54	**56->27**	107->85
African Derived Amerindians										
1	male	87	50	coronary	5+10+20	96->98	6->5	**34->49**	**62->60**	88->80
2	male	85	45	coronary	5+10+20	116->84	8->10	69->50	**68->63**	67->64
3	female	120	48	coronary	5+10+20	93->81	6->8	**51->38**	61->45	103->86
4	male	60	64	coronary	5+10+20	70->73	12->13	**56->57**	53->55	92->70
5	male	54	56	coronary	5+10+20	137->82	6->5	na	78->35	98->78
6	female	70	58	coronary	5+10+20	116->90	70->59	**76->68**	53->46	105->85
7	female	68	65	aort. valve	5+10+20	91-80	52->49	59->45	**60->60**	90->70
8	male	73	67	av-valves	5+10+20	85->73	31->28	**45->54**	43->24	64->55

Fixed doses of Esmolol, based on the pilot studies, were subsequently administered to eight Amerindian Brazilian patients. mg/dose: mg Esmolol per single dose; mmHg: millimetres of mercury; mN: milliNewtons; b/min: beats per minute; developed force: systolic minus diastolic values in milliNewtons; the unloading type of forces are listed on a clear background; the auxotonic type of forces are listed on a shaded background; na: not available.

pilot doses of Esmolol, seeking to establish the most appropriate regime. Thus, the first patient received a bolus of 100 mg, the second a bolus of 50 mg, the third two boluses of 50 mg each, followed by two boluses of 25 mg each. We gave one bolus of 50 mg to the fourth patient, and a bolus of 40 mg to the last patient. Extracorporeal circulation was started 5 min after the last injection, and routine surgery was continued after the force probes had been removed.

In our second series, prompted by the most variable dose-related response of the first group of patients, we investigated, using markedly lower but rising doses, a further cohort of eight Amerindian patients, five male and three female, aged from 45 to 67 years, with a mean age of 57 years. These patients, in six instances, were undergoing surgery for coronary arterial disease, while the remaining two patients underwent aortic valvar plasty and mitral and tricuspid valvar plasty, respectively. These patients all signed informed consent consistent with the institutional policy of the Hospital Geral de Roraima, Boa Vista, Brazil. The force probes were implanted as in the initial cohort. In the first patient of this second cohort, signals recorded from both probes were of the unloading type. Otherwise, as was our intention, the probes recorded either auxotonic or unloading signals. In six patients, we assessed left ventricular pressure using a catheter-tipped manometer implanted through the left ventricular apex. In the other two patients, arterial pressure was measured via the radial artery, as in the first cohort of patients. After a control recording, doses of 5, 10, and 20 mg Esmolol were given intravenously, with an interval of 3 min between the injections. Thereafter, surgery proceeded as described above.

3. Definitions

Since our study reveals aspects of ventricular mechanics that may, to some readers, seem divorced from conventional wisdom, it may be helpful if we provide precise definitions of the terms to be used in the subsequent descriptions.

Tensile force (F_T), calibrated in milliNewtons, is the value measured using the needle probes [1]. After the insertion of the probe, which is 1.5 mm thick and 9 mm long (Fig. 1), some of the aggregated myocytes impinge on the flexible bar in the lateral window of the probe, providing a periodic force signal (Fig. 2). The signal corresponds to the force that acts during contraction of the myocytes that are spread around the lateral window (Fig. 1). As the mesh of myocytes is slightly spread by the thickness of the probe itself, the signal has a constant diastolic component, which serves as the diastolic control. The second, variable, component of the signal corresponds to the tension generated by the contraction of the myocytes during systole.

The developed tensile force is evaluated as the systolic minus the diastolic value.

In classical physiology, the unloading type of signal, designated $F_{T\,unload}$, is the force that exhibits a pronounced drop during the period of shortening of the aggregated myocytes along their long axis [1] (Fig. 2), thus heralding a decrease in afterload. In contrast, the auxotonic, or augmenting, type of signal, designated $F_{T\,auxoton}$, is the force that increases during the period of ventricular constriction because the load coupled to the measured population of myocytes also increases (Fig. 2). We have shown previously that the unloading signal is recorded when the probe is coupled to myocytes that are aggregated with their long axes tangential to the epicardial surface of the ventricular wall [1]. They are unloaded while ventricular radius shrinks. Auxotonic, or augmenting, forces are recorded from myocytes aggregated in an oblique fashion, thus being exposed to augmentation of the load while mural thickness increases. When inserting the probes, however, there is no indicator predicting to which population the probes are coupled. The type of signal obtained after

impalement of the probe, therefore, cannot be predicted with accuracy. As shown by our previous histological study [1], nonetheless, the probability of coupling the probe to obliquely aggregated myocytes, and hence to record an auxotonic signal, is greater in deeper mural zones than in the subepicardial regions.

Antagonism is the term we use to describe the dualistic contractile behaviour of the ventricular myocardium, the tangential myocardial alignment sustaining a strictly constrictive action, while the myocytes orientated with their long axes running obliquely from the epicardium to the endocardium partially counteract the mural thickening. Antagonism implies that not all the contractile forces generated by the ventricular wall act to sustain ventricular emptying. The presence of the greater amount of myocytes being aggregated tangentially, while a smaller, yet significant, number of myocytes aligned with oblique orientation, all of them acting synchronously, serves to put the wall itself under stress from all directions, thus providing self-buttressing and hence stabilising ventricular shape and size. In the setting of myocardial fibrosis, as seen in patients with ischaemic heart disease, we measured the incidence of auxotonic forces to be markedly greater than in non-ischaemic hearts. We assume, therefore, that the supporting matrix of connective tissue, both in health and disease, plays a pivotal role by deviating forces in an oblique direction from the epicardium to the endocardium.

4. Statistical analysis

All values are expressed as means plus or minus standard deviations. We used the Wilcoxon test to determine statistical significance, along with the Mann—Whitney *U*-test for unpaired data. A probability value of p less than 0.05 was considered significant.

5. Results

5.1. Pilot cohort of patients

The systolic arterial pressures dropped to various extents subsequent to beta-blockade at various doses, as shown in Table 1. Marked decreases in end-diastolic arterial pressure were seen in three of the five patients, and unloading forces were also recorded only in three of the five patients. In these three, the force remaining unchanged in the second patient subsequent to beta-blockade (Fig. 3), but dropping by 22% in the first patient and by half in the fifth patient (Table 1). This latter patient, receiving only 40 mg Esmolol, had the most pronounced drop in heart rate of all 13 patients, associated also with a marked drop both in systolic and diastolic arterial pressures. We measured auxotonic signals at seven sites of impalement. These signals decreased by 40% in the first and second patients (Fig. 3), by 30% and 16% in the third patient, by 14% and 23% in the fourth patient, and by 23% in the fifth patient (Table 1). Heart rate decreased in all patients, albeit to markedly varying degrees (Table 1).

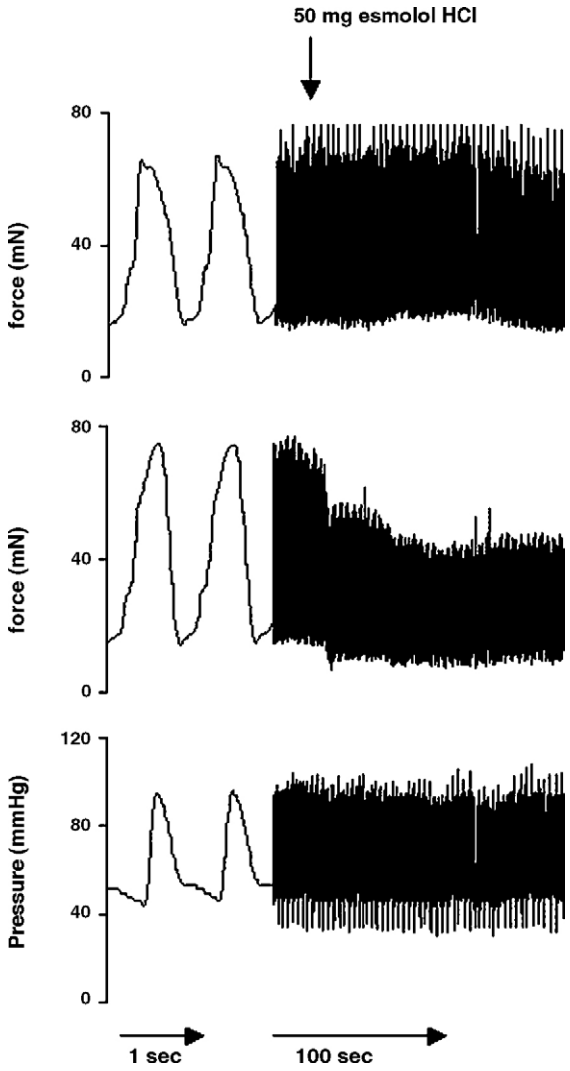

Fig. 3. A recording under control conditions from the second patient of our first cohort, showing the unloading type of contractile force recorded from some tangentially aggregated myocytes (upper trace), the auxotonic type of forces recorded from the myocytes aggregated obliquely from epicardium to endocardium (middle trace), and the pressure in the radial artery (lower trace), the changes being induced by a single dose of 50 mg Esmolol. Note the drop in the auxotonic force, shown in the middle trace, subsequent to administration of Esmolol, and the absence of any drop in the unloading type of force (upper trace).

5.2. Second cohort of patients

Although using appreciably smaller doses of Esmolol, we noted heterogeneous responses of the systolic and end-diastolic left ventricular and arterial pressures, respectively, with the heart rate decreasing to varying extent in all patients. Overall, the haemodynamic alterations were statistically insignificant (Table 1). We recorded an unloading type of force in all eight patients. Subsequent to beta-blockade, the measured force remained unchanged in four, fell in two and increased in two (Table 1, Fig. 4). Auxotonic forces were measured in seven of the eight patients. Mean values of these forces dropped significantly in all but the fourth patient (Table 1, Fig. 4). Positive dF/dt_{max}, as measured in the patients making up the second cohort of

eight patients, dropped to a greater extent in the auxotonic than in the unloading type of forces, while for negative dF/dt_{max}, the differences were less pronounced (Fig. 4). None of the changes in velocity of rise, nor that in decline, either for the auxotonic or the unloading type of forces, became statistical significant when related to control conditions.

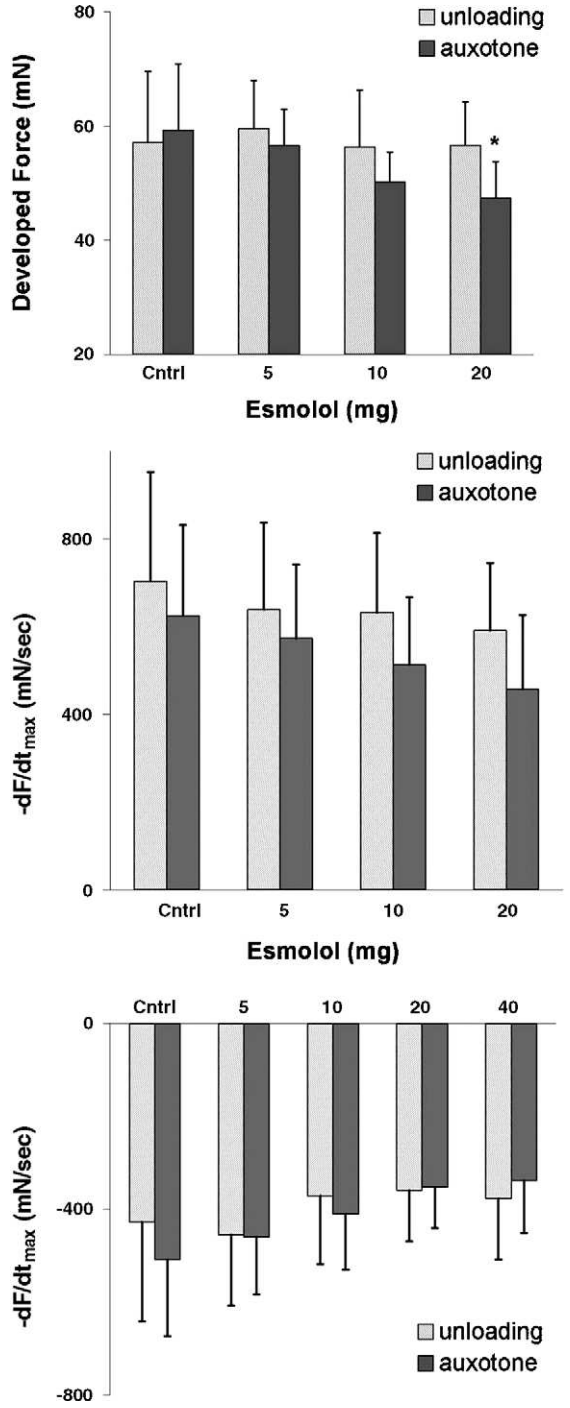

Fig. 4. The upper panel shows the changes in myocardial forces seen in the eight patients making up our second cohort subsequent to administration of 5, 10, and 20 mg of Esmolol. Note that the drop in auxotonic forces at 20 mg Esmolol is significant (*) relative to control values, and also relative to some inconsistent changes in the unloading type of forces. The middle panel shows the response of positive dF/dt_{max} assessed in the auxotonic and unloading forces. The lower panel shows the response of negative dF/dt_{max} in both types of forces. Note that the changes in velocity of rise and decline of both forces with none of the dosages used become statistical significant relative to control conditions.

6. Discussion

To our knowledge, the capacity of drugs, such as barbiturates, to depress contractile forces depending on the afterload exerted on the myocytes has attracted little, if any, attention [1]. If we are to understand their therapeutic actions, we must first appreciate the way the myocytes are arranged within the ventricular walls. In this respect, we have shown previously that the amount and the slope of afterload of an individual myocyte are determined not only by the global haemodynamic resistance of the ventricular outflow, but are also the consequence of the geometrical alignment of the individual myocytes within the ventricular myocardial mesh [1].

The overall anatomic arrangement of the ventricular walls is that of a three-dimensional mesh of myocytes set in a matrix of fibrous tissue, the myocytes themselves being aggregated such that their long axes either run tangentially or obliquely relative to the thickness of the ventricular wall [2–4]. This arrangement permits the contraction of the aggregated myocytes to create antagonism through the interaction of unloading and auxotonic forces [1]. The amount of the auxotonic forces engendered by the myocytes aggregated with their long axes obliquely through the short axis of the wall is a function of their inclination, together with the thickness of the wall. The thicker the wall becomes at end-systole, the more the myocytes are inclined relative to the short axis. Hence, the greater is the increment of the auxotonic forces as the myocytes are deviated in a direction from the epicardium to the endocardium [2–4], and the more they counteract the systolic mural thickening [1]. Under physiological conditions, these two opposing forces provide balance for the entirety of the ventricular walls, contributing both to the stability of ventricular shape and the cavity size [1–3]. As myocardial structure and function are organised in an antagonistic fashion, we needed to make focal measurements of contractile activity to determine if the active state of contraction of myocytes aggregated in oblique fashion persists longer than the period of contraction of the myocytes aggregated with their long axes tangential to the wall. As these measurements showed, the contraction of the obliquely aggregated myocytes does indeed persist beyond the end of ejection. We presume, therefore, that the obliquely orientated myocytes are able to act during the beginning of diastole so as to enhance ventricular dilatation [1]. When considering this action in the setting of known clinical data [10], we infer that the primarily beneficial antagonistic regulation of the dual contractile activity becomes unbalanced in the setting of congestive heart failure. In the setting of systemic hypertension, for example, we infer that, initially, it is only the constrictive performance of the tangentially aggregated myocytes that is increased. This results in an increase in mural thickness, which then additionally increases the loading of those myocytes aggregated obliquely relative to the thickness of the wall, and hence also promotes their own hypertrophy. Concomitant with this increase in mural thickness, both arms of the

antagonistic system load one another incrementally, thus providing a stimulus for further hypertrophy in both populations of myocytes. The key to the therapeutic success of interrupting the vicious circle inherent in this setting, therefore, could be to attenuate selectively the dilatory arm while preserving the constrictive activity of the tangential population of myocytes.

Beta-blockade, despite its known negative inotropic effect, has recently been shown to improve global ventricular function when administered over the long term to patients with cardiac failure of mild and moderate degree [6—10]. This seemingly paradoxical action has been explained on the basis of a time-consuming, yet progressive suspension of the prevailing down-regulation of beta-receptors [6—9]. Our current results now suggest that an additional mechanism could be involved. We postulate that beta-blockade, at low doses, exerts an instantaneous selective action, which constrains the forces engendered by those myocytes which are aggregated with their long axes oblique relative to the short axis of the ventricular wall. These aggregated myocytes, as we have shown, are more sensitive to the depressant action of beta-blockade than the prevailing tangentially aggregated myocytes, the latter cells engendering the constrictive activity [1—3].

In the majority of our patients, however, our chosen doses were such as to provide unintentional dual relief in contractility, mediating also a drop in systemic systolic pressure. This shows that, for most of the patients, these chosen doses were too high, since they also attenuated the action of those prevailing tangential aggregates of myocytes that sustain ventricular ejection and/or reduce also systemic vascular resistance. On the other hand, we anticipate that, in an antagonistic system, the attenuation of the one arm indirectly also unloads the other opposing arm. This effect would explain our observed findings in some patients of a concomitant drop in unloading forces without any decline in arterial pressure. The significance of such potential mutual interaction of the two arms of intramural myocardial antagonism must as yet remain speculation because, for methodological constraints, we are unable to measure both activities confocally at their common site of action. Our findings nonetheless confirm the obliquely orientated myocytes, which contract auxotonically, to be the primary target of Esmolol when this drug is given in low doses. The findings also point to the need for a more extended study exploring appropriate doses. A clinical trial would also be justified to show that beta-blockade, given at low dosage over the long term, is able to sustain the selective attenuation of the auxotonic arm of the intramural myocardial antagonism.

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